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FORMULATION AND EVALUATION OF DOXOFYLLINE BUCCAL PATCHES

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ABSTRACT

The objective of present study was to develop matrix type buccal patch therapeutic systems of Doxofylline using sodium alginate, ethylcellulose, and hydroxypropyl methylcellulose in various proportions and combinations were fabricated by solvent casting technique. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption, in vitro drug release studies were evaluated. An *in vitro* drug release study was designed, and it was carried out using commercial semipermeable membrane. The F4 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 97.35%, 95.35%, 94.26%, 98.60%. were obtained during in vitro drug release studies after 20 hrs. The release of Doxofylline appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F4 formulation was concluded as optimized formulation.

KEYWORDS: Buccal delivery system, Natural and synthetic polymers, solvent casting technique, Diffusion mechanism.

INTRODUCTION

Buccal route of drug administration occurs from their ability to enhance the bioavailability of the drug impaired by narrow absorption windows in the gastrointestinal tracts. Mucoadhesion has become of interest for its systemic delivery by retaining a formulation intimate contact

with buccal cavity.[1,2] Drug delivery of buccal route provides the direct entry to the systemic circulation through the jugular vein by passing the first pass hepatic metabolism leading to high bioavailability. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration.[3,4] The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries.[5,6] Doxofylline is a xanthine derivative drug used in the treatment of asthma. Doxofylline mechanism of action is related to the inhibition of phosphodiesterase activities, resulting in bronchodilating effects. The aim of the present study was to formulate and characterize buccal patches containing doxofylline containing polymers. Doxofylline buccal patches evaluated, thickness, folding endurance, moisture absorption, moisture loss, weight variation, in vitro drug release, and stability were examined.[8] Buccal patches of doxofylline may provide sustained buccal delivery of doxofylline for a long with polymers and by pass of the gastrointestinal tract and hepatic portal system and orally administered drugs bioavailability enhanced that otherwise undergo hepatic first metabolism.[7,8]

MATERIALS AND METHOD

MATERIALS

The chemicals were obtained from different sources. Doxofylline gifted sample from Hetero labs Hyderabad, Sodium alginate, Ethylcellulose, Eudragit gifted from SD fine chemicals. Polyethylene glycol and methanl gifeted from AR chemicals Hyderabad.

METHODOLOGY[9,10,11]

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were

exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Formulation design

Preparation of buccal patches

Transdermal patches containing Doxofylline were prepared by the solvent casting evaporation technique. The drug Doxofylline was dissolved in methanol. Polymers HPMC, Ethylcellulose and Sodium alginate were taken in a beaker, to this add Doxofylline drug which was previously dissolved in methanol. Sufficient care was taken to prevent the formation of lumps. The beaker was kept under magnetic stirrer. PEG was taken as a plasticizer and DMSO added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate ($40cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Table 1: Formulation Design of Buccal Patches

S. No	Formulation code	Ingredients (mg)			
		Drug (mg)	HPMC	Ethylcellulose	Sodium alginate
1	F1	100	1000	-	-
2	F2	100	-	1000	-
3	F3	100	-	-	1000
4	F4	100	500	-	500

Evaluation of Buccal patch formulation[12,13]

Physico- chemical evaluation

Physical appearance

All the prepared Doxofyline films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity

The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 $cm^2$of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The buccal films (2 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 209 nm. Similarly a blank was prepared from buccal films without drug.

$$\text{Drug content} = \frac{\text{Weight of drug in patch}}{\text{Total weight of patch}} \times 100$$

Moisture absorption studies

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

in-vitro Drug release studies

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically at 209 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

Stability studies

Optimized medicated films were subjected to short term stability testing. The buccal films were sealed in Aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

RESULTS

Drug and excipient compatability studies (FTIR)

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

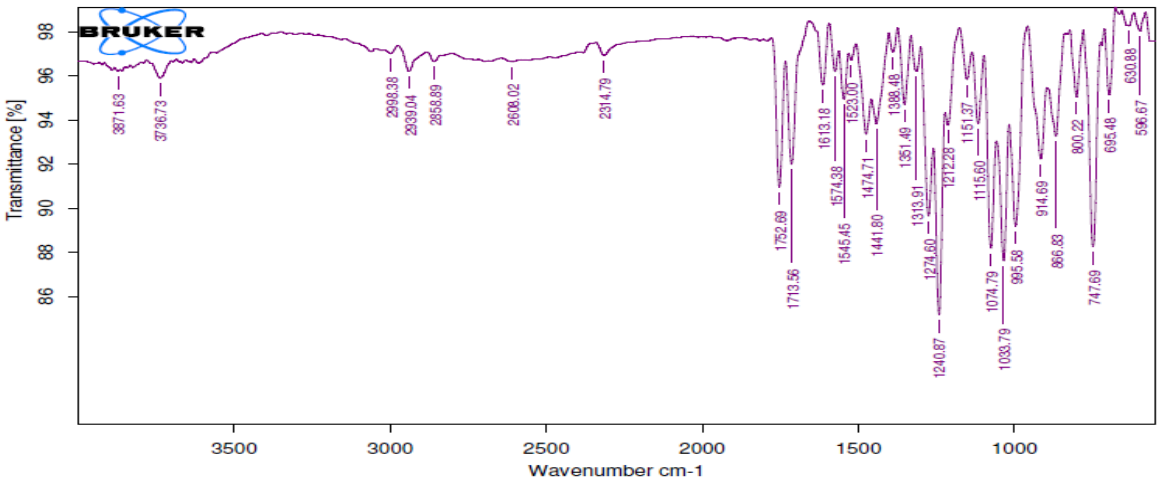

Fig. 1: FT-IR graph for Pure drug.

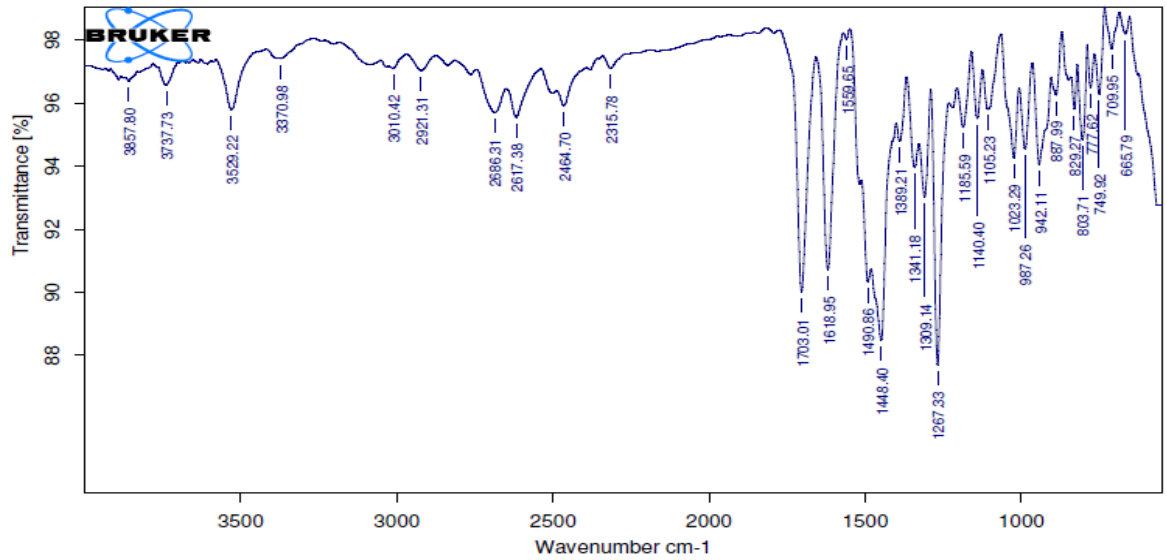

Fig. 2: FT-IR graph for Optimized formulation.

Physical appearance and surface texture of patches

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight uniformity of patches

The weight of the patches was determined using digital balance and the average weight of all patches.

Thickness of patches

The thickness of the patches was measured using screw gauge and the average thickness of all patches.

Folding endurance of patches

The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Moisture Loss

The moisture content (%) study was done for 3 days. In most cases, the moisture uptake content was found to increase with increasing concentration of polymers that are more

hydrophilic in nature. The low moisture content in the formulation is highly appreciable to protect from microbial contaminations and bulkiness of the patches. Again, a low moisture content in formulations helps them to remain stable from being a completely dried and brittle patch.

Moisture uptake

The moisture uptake (%) study of various films was done at high relative humidity like 76% and 86% for a period of 3 days. In all cases, the moisture uptake was found to increase with increase in relative humidity. The low moisture uptake by all these formulations was observed at various levels of relative humidity. This low moisture uptake (%) by doxofylline buccal patches can help to retard any hydrolytic degradation, and patches will remain stable.

Surface pH of patches

Surface pH was determined by bring the patches in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrate for 1 min and the average surface pH of all patches.

Drug content uniformity of patches

Doxofylline buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated.

Table 2: Physicochemical evaluation data of Doxofylline Buccal Patches.

Formulation code	F1	F2	F3	F4
Thickness (mm)	0.22	0.24	0.25	0.26
Weight variation (mg)	2.64	2.85	2.90	2.69
Drug content Uniformity	94.55	95.70	95.68	97.56
Folding endurance	81	80	84	82
Surface pH	4.5	4.8	4.6	4.2
Moisture loss	1.15	1.21	1.26	1.24
Moisture absorption	4.39	4.32	4.35	4.55

Table 3: In vitro diffusion studies.

Time (hrs)	Cumulative % drug release			
	F1	F2	F3	F4
0	0	0	0	0
1	9.45	8.42	10.11	12.54
2	12.20	11.26	12.30	14.25
3	19.12	18.10	17.12	19.99

4	22.85	20.26	19.35	24.56
5	29.30	25.26	24.50	30.55
6	31.90	32.55	30.45	35.25
7	39.78	35.25	34.29	40.26
8	42.72	40.51	39.55	45.60
9	53.38	54.20	51.19	55.55
10	61.55	60.29	59.30	62.22
11	66.39	64.39	62.40	68.25
12	70.56	69.25	68.32	72.56
13	72.29	71.30	70.24	79.52
14	79.63	78.25	77.19	82.55
15	82.36	81.40	80.25	86.30
16	85.65	84.55	81.60	89.52
17	89.39	88.56	87.10	91.21
18	91.25	90.30	89.28	93.55
19	93.96	91.25	90.18	95.65
20	97.35	95.35	95.35	98.60

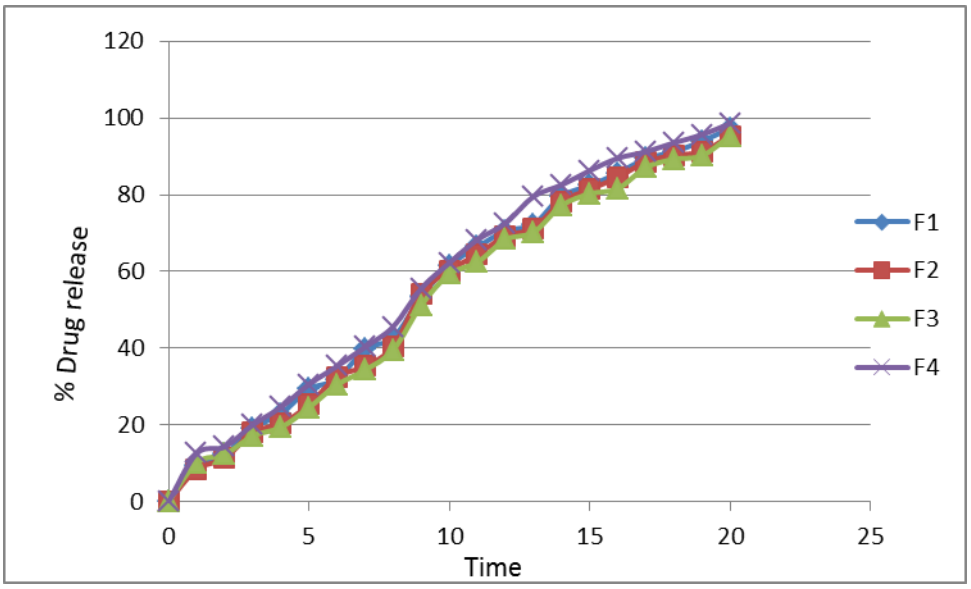

Fig. 3: Dissolution study for All formulation.

Stability studies

Table 4: Stability study of Optimized Formulation.

Formulation Code	Initial	1st Month
F4	98.60	98.55
F4	98.60	98.54
F4	98.60	98.58

CONCLUSION

From the present research work that is development and evaluation of Doxofylline patches for buccal drug delivery, the following points can be concluded. The patches prepared were

elegant in appearance and smooth surface. The weights of patches were uniform. The thicknesses of patches were uniform. The patches were completely dried. The patches had good flexibility. The surface pH of the patches was uniform. There was no drug-excipients interaction between the drug and excipients used in the formulation. The drug was distributed throughout the patch uniformly. More than 85 % of the drug was released from all the formulations at the end of 20hrs. In short term stability studies indicate there were no significant changes in the drug content and *in-vitro* drug release for the period of one month. From the result and conclusion of the research work we can summarize that Doxofylline can be delivered via buccal route.

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